LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

REMARKS

The Office Action of September 27, 2001 has been carefully considered.

Proper subject matter headings have been added to the specification.

Claims 1-21 have been rejected under 35 USC 112, 2nd paragraph, on several grounds.

In claim 1, a question is raised as to the meaning of "regular stack of concentric bilayers." This language is intended to describe the onion-like structure disclosed in the present specification at page 6, line 30 through page 7, line 13, and previously described in WO 93/19735 and WO 95/18601, corresponding, respectively, to US 5792472 and US 6103259. The structure is further described on page 9 of the specification, lines 11-36.

In light of this description is the specification and in the prior art, Applicants submit that those of ordinary skill in the art understand the terminology used in claim 1.

Objection has also been raised to "avoiding" in claim 1, and this has now been changed to "inhibiting."

The surfactant in claim 5 is in addition to the surfactant recited in claim 1, and this has now been clarified.

In claim 7, "trapping" has been changed to "sequestering" in accordance with the original French term "sequestrant" on

page 11, line 9 of corresponding published PCT application WO 99/27907.

Claim 15 is thought to be clear as written, the composition including a second active agent, which also serves as a stabilizer for the first active agent.

A question has been raised regarding the "leakproofing" agent of claim 16. This claim has now been amended to recite an agent for enhancing "leaktightness" of the vesicles. This is in accordance with the original term "etancheite" of the French specification, which translates as "tightness" in the sense of avoiding leaks.

The Office Action states that claim 17 should be amended to recite the method of preparing the lamellar phase. Applicants disagree on the basis that this step is known to those of ordinary skill in the art, and is described in the references cited in the specification. Moreover, it is well known in the art that a lamellar phase is under thermodynamic equilibrium, and the choice of method used for its preparation has no influence on the result. Only the macroscopic conditions (temperature, pressure, composition) have an influence on the nature of the resulting phase.

Thus, the method of preparation of the lamellar phase is best left to those of ordinary skill in the art based on the knowledge of the art.

Claim 20 has been amended to delete the terminology which should have been deleted in the first amendment.

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

Withdrawal of this rejection is requested.

Claims 1-18 have been rejected under the judicially created doctrine of obviousness type double patenting over claims 1-26 of US 5,908,697 and also rejected over claim 12 of US 6,277,404.

The cited patents relate to uses for the vesicles also used in the presently claimed invention. There is, however, no suggestion in the cited references to incorporate in the vesicles an active compound together with a compound for inhibiting the degradation of the active compound. Thus, the invention is not obvious based on the claims of the cited references, and withdrawal of these rejections is requested.

Claims 1-3 and 5 have been rejected under 35 USC 102(b) over CA 2133421.

The Canadian reference is directed to vesicles of the same type as those presently claimed, and disclose stabilization of the structure of the vesicles by reinforcing their rigidity with a polymer. This is purely a physical effect, and there is no disclosure or suggestion of stabilizing the active substance with is incorporated in the vesicles by incorporation of a stabilizing agent.

Withdrawal of this rejection is requested.

Claims 1-8 and 14-16 have been rejected under 35 USC 102(b) over WO 96/31194.

The reference discloses multilamellar, non-phospholipid liposomes which incorporate a retinoid and a stabilizing

system therefor. These liposomes are classical liposomes, and specifically are paucilamellar liposomes constituted by a few bilayers surrounding a core. A definition of the liposomes is given in the last paragraph on page 11, the liposomes being closed structures composed of curved lipid bilayers which entrap a part of the solvent in which they freely float into their interior.

There are thus two important differences with the vesicles of the present invention:

the liposomes of the prior art include an interior medium, whereas the liposomes of the invention include an aqueous medium which alternates continuously with the lipophilic medium; and

the liposomes of the prior art are manufactured in suspension, and are thus in a non-equilibrium state, whereas the liposomes of the invention are under a thermodynamic equilibrium.

Thus, the liposomes of this reference are classical liposomes which do not have the presently claimed structure, and there is no disclosure or suggestion in this reference of replacing those liposomes with the liposomes of the invention.

Withdrawal of this rejection is requested.

Claims 1-8 and 14-19 have been rejected under 35 USC 102(b) over WO 95/18601.

This reference relates to a method for preparing the vesicles having the structure of those of the invention.

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

However, there is no disclosure of encapsulating within such vesicles an active agent together with an agent to inhibit degradation of the active agent. Withdrawal of this rejection is requested.

Claims 1-7 and 9-21 have been rejected under 35 USC 102(b) over Munechika et al.

This reference discloses multilamellar liposomes containing lecithin, a surfactant and an enzyme. The vesicles may further contain stearylamine, cholesterol and polysaccharides as stabilizers (col. 3, lines 5-7), but these substances are used to physically stabilize the structure of the vesicle, and not to prevent degradation of an active ingredient enclosed within the liposomes. There is also a teaching of the use of an antioxidant to stabilize the lipid (col. 2, line 60) but this is not a teaching of adding a stabilizer for the drug in the vesicles. Regarding the stability of the incorporated drug, it is disclosed that the method itself increases the stability of the drug (col. 1, lines 51-56) but there is no teaching of adding a stabilizer for the drug incorporated within the liposomes.

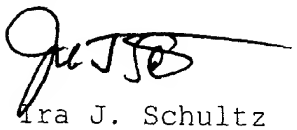
Thus, there is no teaching in Munechika et al of the claimed invention, and withdrawal of this rejection is requested.

In view of the foregoing amendments and remarks, Applicants submit that this application is now in condition for allowance. An early allowance of the application with

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

amended claims is earnestly solicited.

Respectfully submitted,



Ira J. Schultz
Registration No. 28666

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

APPENDIX

IN THE SPECIFICATION:

Page 22, lines 25-26: [These examples also make reference to Figures 1 to 4:] BRIEF DESCRIPTION OF THE DRAWINGS

IN THE CLAIMS:

1. (Twice Amended) A composition containing an active agent encapsulated within multilamellar vesicles in the form of a regular stack of concentric bi-layers comprising at least one surfactant, said bi-layers extending from each vesicle core to periphery, and being separated by an interstitial liquid, wherein said vesicles contain at least one agent for [avoiding the] inhibiting degradation of said active agent.

5. (Twice Amended) The composition according to claim 1, wherein said bi-layers of the vesicles further contain at least one polymer surfactant or a polymer having amphiphilic properties.

7. (Twice Amended) The composition according to claim 1, wherein said active agent is a substance sensitive to oxidation and said agent for [avoiding] inhibiting degradation is a substance having reducing properties, having a [trapping] sequestering effect or which acts on pH when the redox potential depends on pH.

16. (Twice Amended) The composition according to claim 1, wherein said vesicles further comprise at least one

[leakproofing] agent <u>for enhancing leaktightness of the vesicles</u>, said [leakproofing] <u>at least one</u> agent being encapsulated within said vesicles or comprising an external coating on said vesicles.

20. (Twice Amended) A method of protecting or immobilizing an enzyme, comprising placing said enzyme in the presence of multilamellar vesicles in the form of a regular stack of concentric bi-layers comprising at least one surfactant, said bi-layers extending from each said vesicle core to periphery, and being separated by an interstitial liquid, said vesicles incorporating therein at least one agent for avoiding degradation of said enzyme [as defined in].

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155